



Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants

◀ *Pollution from Personal Actions* ▶

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NOTE

Because of the size of this presentation, this file comprises only the 3rd part of the entire PPCPs slide presentation. The subsequent parts must be accessed separately.

These slides and many additional materials are available at the U.S. EPA's *PPCPs Web Site*:

<http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm>



Exposure to Multiple, Trace-Level PPCPs — Below Human “Therapeutic” Doses

Potential Toxicological Significance Can Exist As a Result of:

- (1) *Risk Cup* body burden: Potential for **additive effects** from multiple agents sharing common MOAs to exceed an effects level. This becomes especially important if the exogenous PPCPs add to a pre-existing burden of endogenous toxicants that share the same MOA.
- (2) Possible **interactive effects**, especially synergism. Drug industry attempts to avoid developing new candidate drugs with potential adverse drug reactions. But the strategy is based upon focusing on those drug combinations that are most probably encountered in practice (e.g., a candidate cardiac drug would be screened against drugs that cardiac patients typically take), as opposed to all drugs (a currently economically infeasible approach).

continued –

Potential Toxicological Significance Can Exist As a Result of:

- (3) **Non-target species receptor repertoires** not as well characterized. Variation in receptor repertoires across species, and unknown overlap with humans leads to countless questions regarding potential effects.
- (4) **Hormesis** – Effects below NOELs. “U-shaped” curves. Data acquired solely at higher “therapeutic” doses (where testing is usually performed) has no predictive capability for the type or amplitude of response at lower concentrations.
- (5) Comparatively little research performed at **extremely low concentrations** (nM-pM and below). Some agents have ability to impart effects at “ultra-trace” concentrations.
- (6) Susceptible **genetic outliers** within species.
- (7) **MOAs not fully understood**. Most drugs can each have a multitude of effects. Most remain to be discovered.

continued –

The “Risk Cup”: Complex and Currently Unresolvable Issues Affecting Regulatory Approaches Aimed at Multiple Exposure / Multiple Effects (graphically summarized on following slide)

Multiple effects (endpoints): Exposure to one chemical having multiple mechanisms/modes of action (MOAs)

Synergism/Antagonism: Unanticipated endpoints (deviating from additive) from interactions of multiple chemicals

Aggregate Exposure: Factoring additive exposure via all pathways and sources for one chemical (cumulation of individually smaller risks); e.g., antibiotics via food residues and drinking water

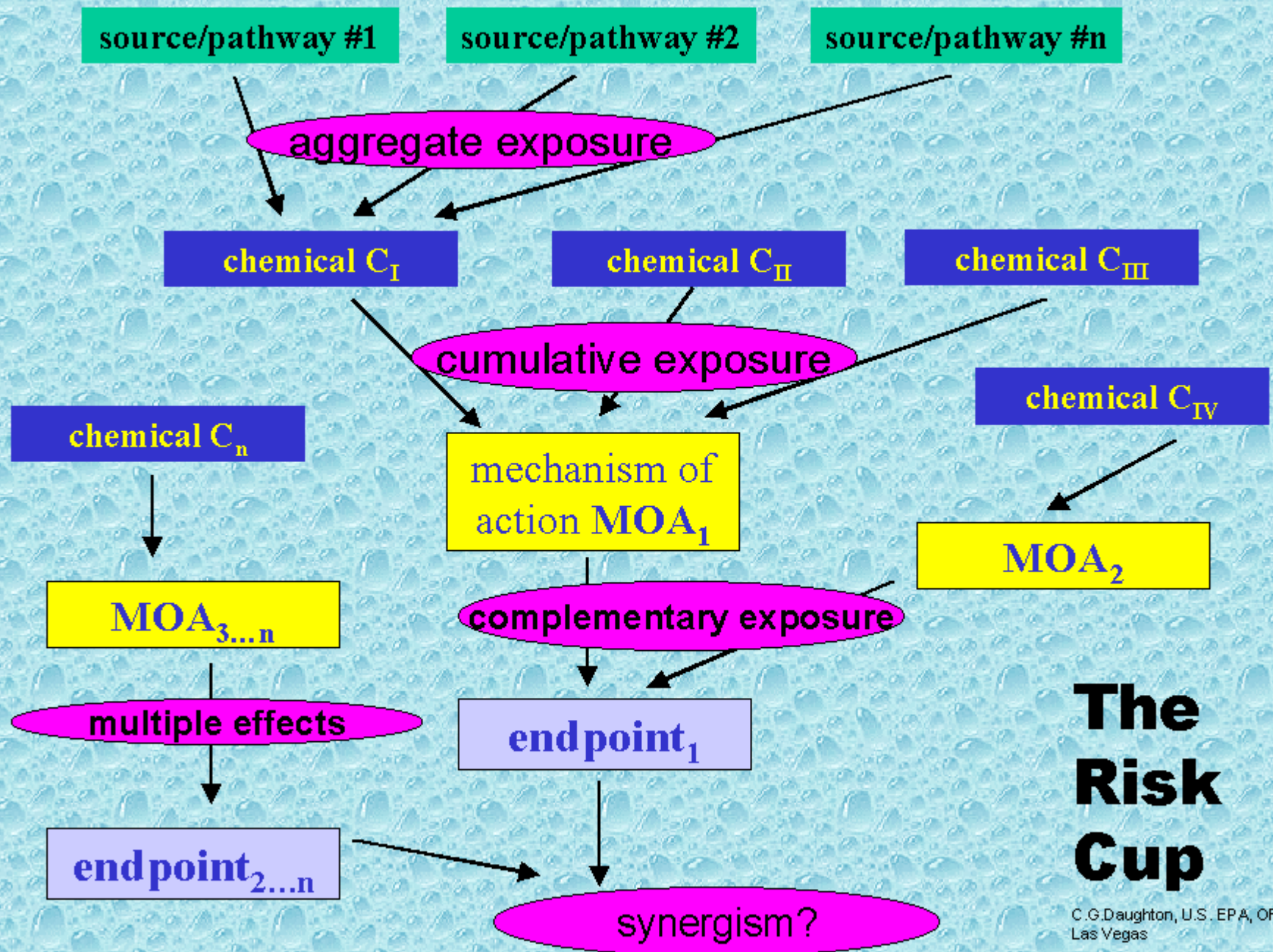
Complementary Exposure: Co-exposure from chemicals acting by different MOAs but yielding similar ultimate endpoints; e.g., all types of antidepressants

Cumulative Exposure: Factoring exposure to multiple chemicals sharing a common MOA; e.g., anticholinergics, selective serotonin reuptake inhibitors, calcium channel blockers

Biological Effects of Low Level Exposure (BELLE): For example, **Hormesis** – paradoxical or unanticipated effect at low doses of a chemical (see: <http://www.belleonline.com/>)

Ultimately, *regulatory decisions are not solely a matter of science* – they must also factor in complex, interacting societal values

continued –



The Risk Cup

C.G. Daughton, U.S. EPA, ORD/NERL,
Las Vegas

February 2001

The Risk Cup

C.G. Daughton, U.S. EPA, ORD/NERL, Las Vegas
February 2001

Multiple exposures to same PPCP

single PPCP:
*e.g.,
tetracycline*

**aggregate
exposure**

Water (contaminated from excrement)
Food (inadvertent drug residues)
Medication

Exposure to multiple PCPPs sharing same MOA

**multiple PPCPs,
same sub-class:**
e.g., SSRIs

**cumulative
exposure**

common, shared MOA
e.g., via serotonin modulation

Exposure to multiple PCPPs sharing same end effect

**multiple PPCPs,
unrelated sub-classes:**
e.g., antibiotics

**complementary
exposure**

different MOAs
*e.g., all resulting in inhibition of microbial
growth*

Exposure to multiple PCPPs resulting in interactive effects

**multiple PPCPs,
unrelated classes:**
e.g., SSRIs & MAOIs

**combined
exposure**

different effects
e.g., resulting in synergism/antagonism

Real-World Demonstration of Synergism from Multiple Stressors

– Extremely Complex Endeavor --

Proper experimental design to conclusively assess synergy is extraordinarily complex.

- ▶ Most published studies attempting to address synergism use **insufficient or flawed experimental design**.
- ▶ Literature is **extremely confusing with respect to definitions** involved with interactions. A diverse spectrum of terms are employed, sometimes in contradictory fashion (sometimes the same term has different, conflicting meanings).
- ▶ Many studies (improperly designed) **erroneously conclude that synergism exists** when the effects are actually additive. Others **fail to uncover synergism** when it is actually present.

continued –

Real-World Demonstration of Synergism from Multiple Stressors

– Extremely Complex Endeavor –

Interactions can be an interactive function of the:

- ▶ amplitude or level of effect selected for study (e.g., 10% level vs. 50%),
- ▶ concentration of the components (as this can change the type of effect – different MOAs),
- ▶ mixture ratios of the individual components (for mixtures, the dose alone is insufficient for defining the poison – also required is the ratio of the doses of the constituents),
- ▶ presence of including naturally occurring toxicants and other endogenous constituents or parameters that have effects of their own – e.g., pH, ionic strength, temperature, etc.),
- ▶ concentration of the receptor used in the assay or measurement,
- ▶ the different biological levels of organization reflected by the measured effect (molecular, sub-cellular, cellular, organ, organism, population, community).

continued –

Biological Effects of Low-Level Exposure - BELLE -

Hormesis: Major aspect of BELLE (<http://www.belleonline.com/>)

Paradoxical or unanticipated effect at low doses of a chemical

Hypothetical, paradoxical phenomenon of seemingly beneficial effects at low doses for chemicals that are otherwise toxic at higher doses

Hormetic: Substance that presents an adverse risk at higher exposure levels but serves to protect at lower exposure levels

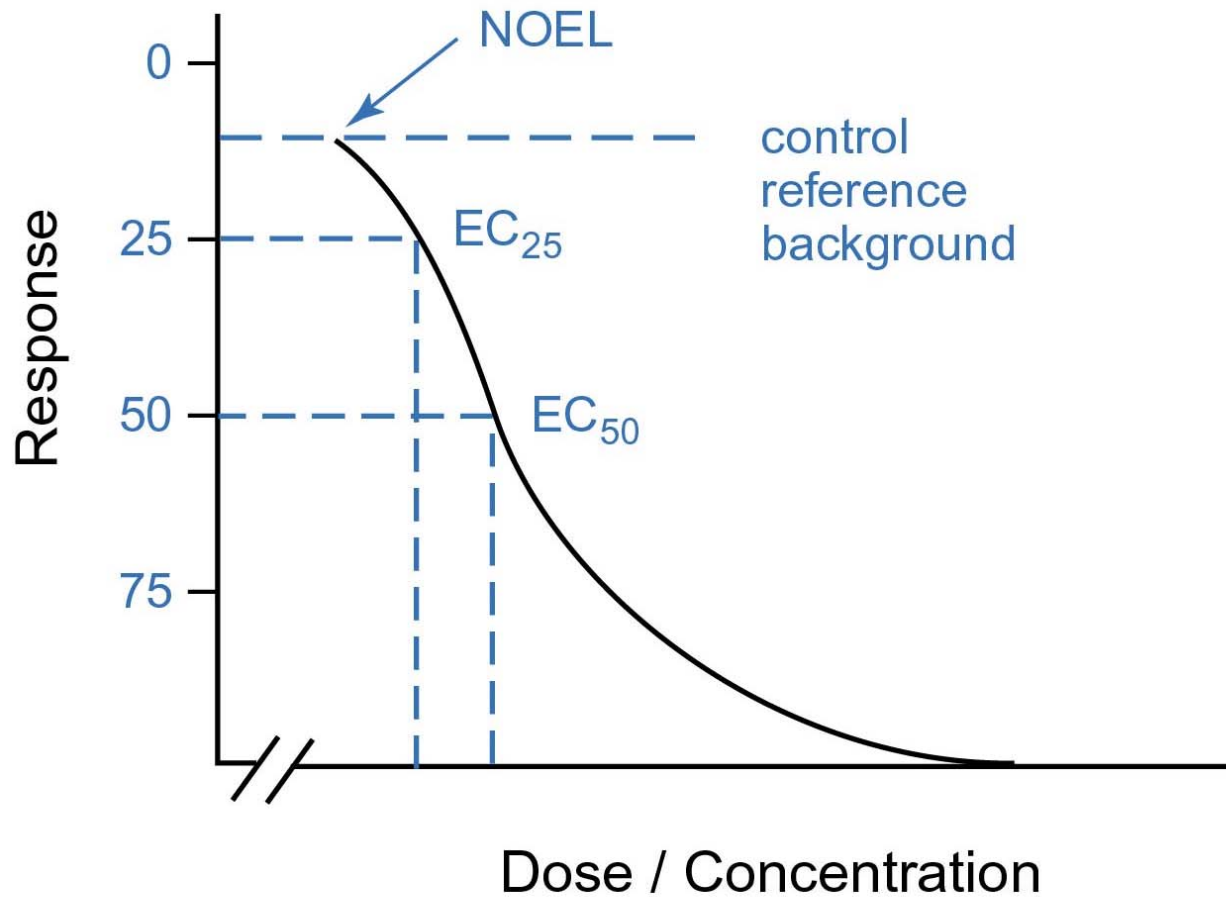
Protection purportedly afforded by a variety of mechanisms including: adaptation, damage repair, and stimulation of biochemical processes (e.g., efflux pumps)

In contraposition to the traditional linear/log-linear low-dose extrapolation model

Scientifically controversial (e.g., U- and inverted U-shaped curves)

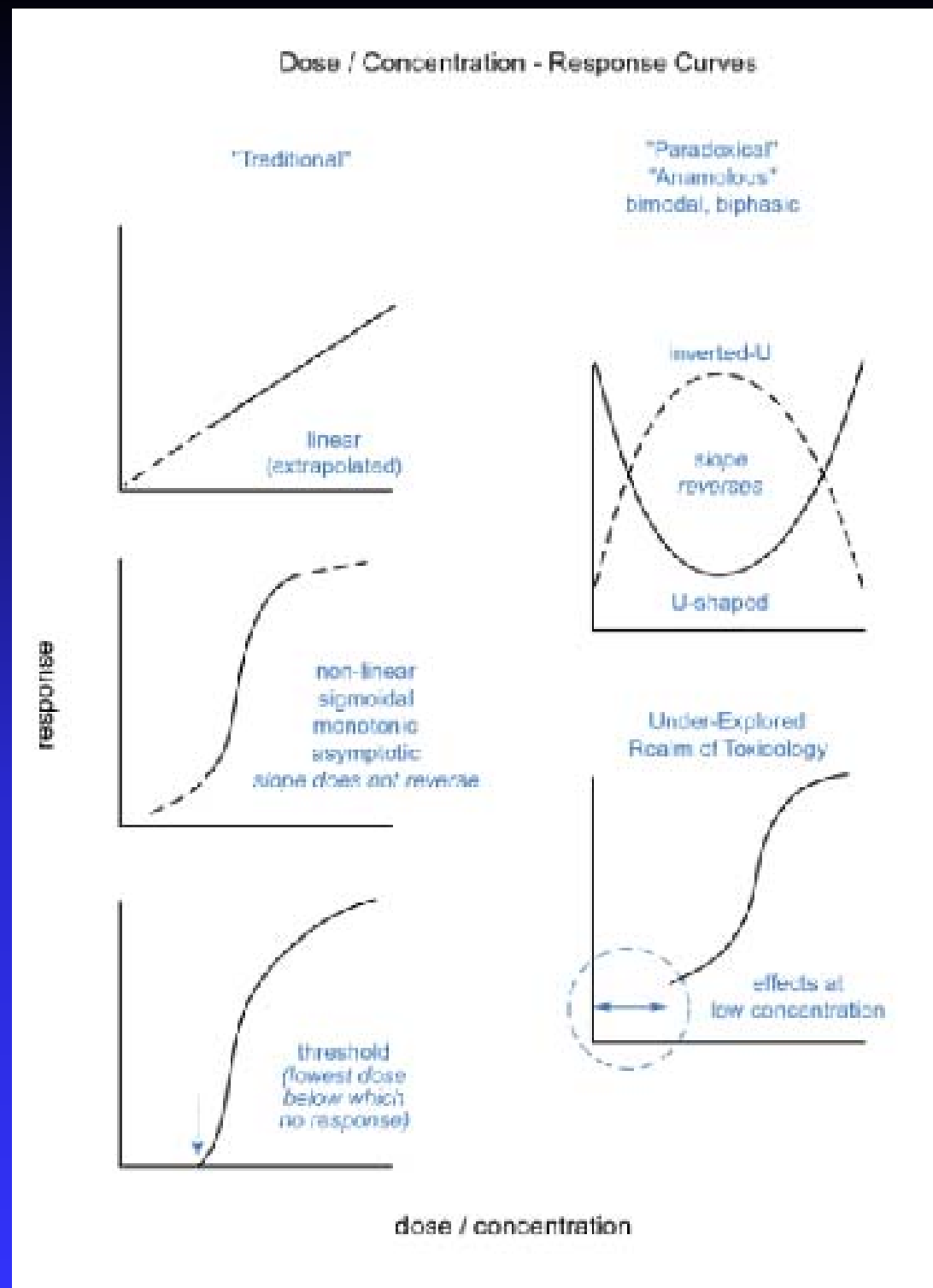
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Sigmoidal Dose Response Curve



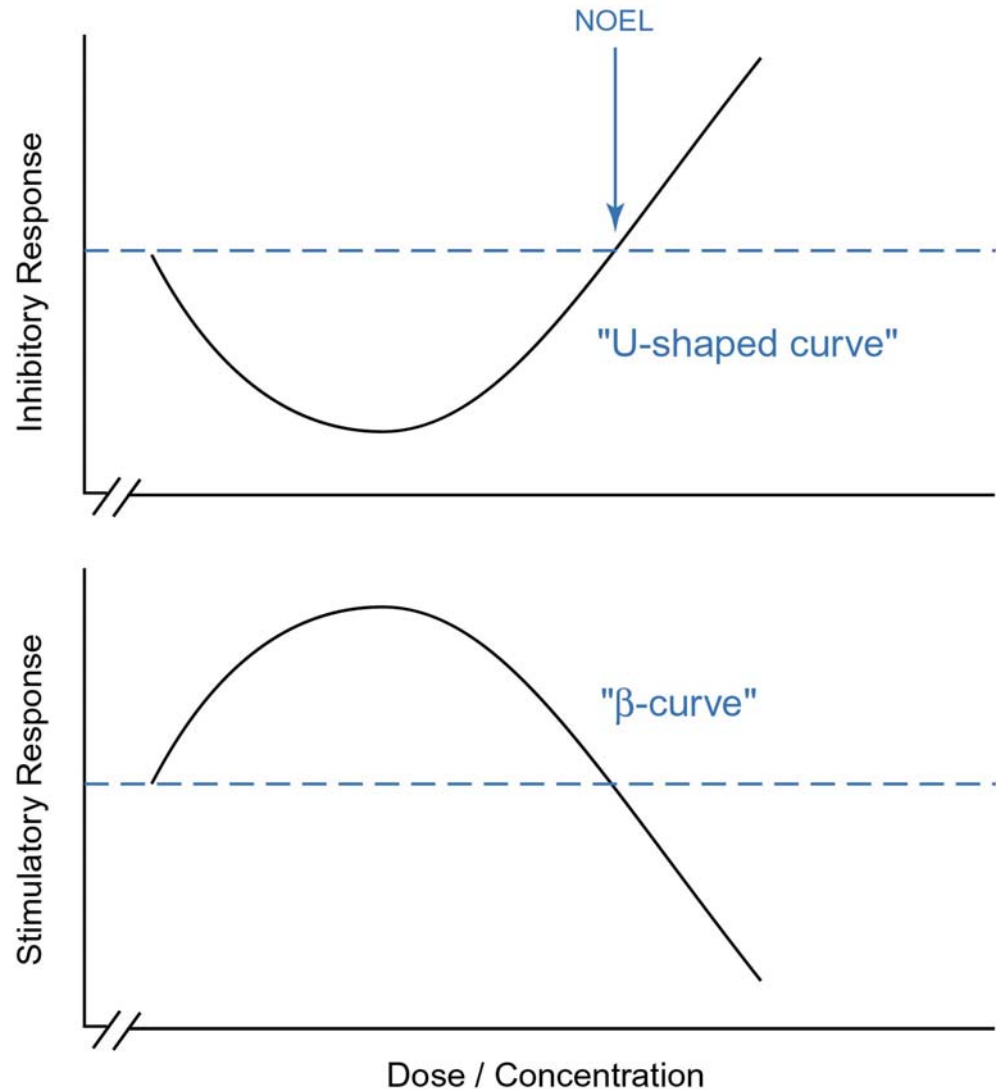
DRCs:

Traditional curves make many assumptions regarding the concentration realm that resides outside the domain of empirical testing.

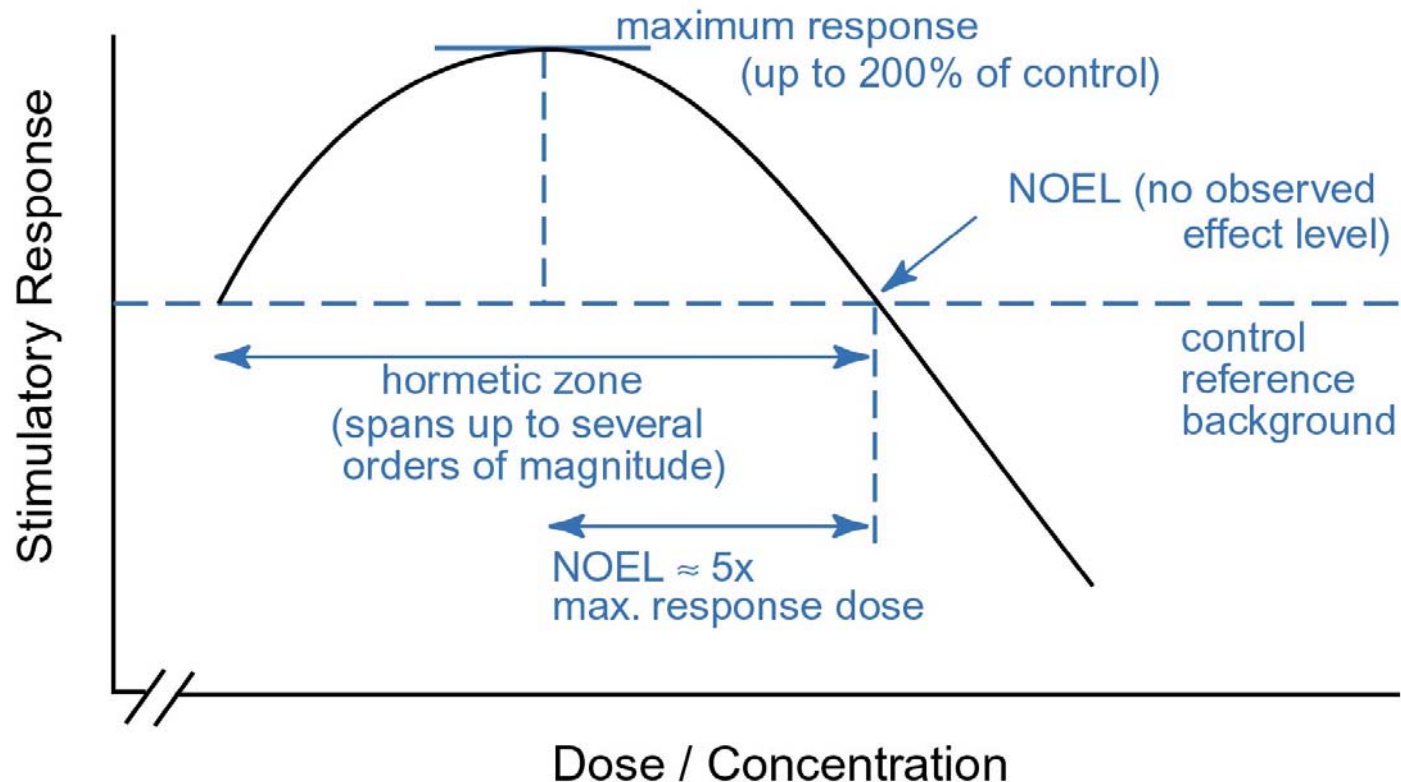


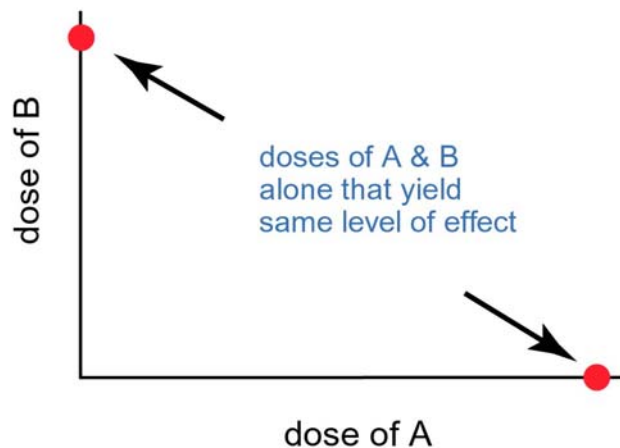
Hormesis may be a common phenomenon — one that frequently goes unnoticed.

"Paradoxical" Response Curves (from hormesis)



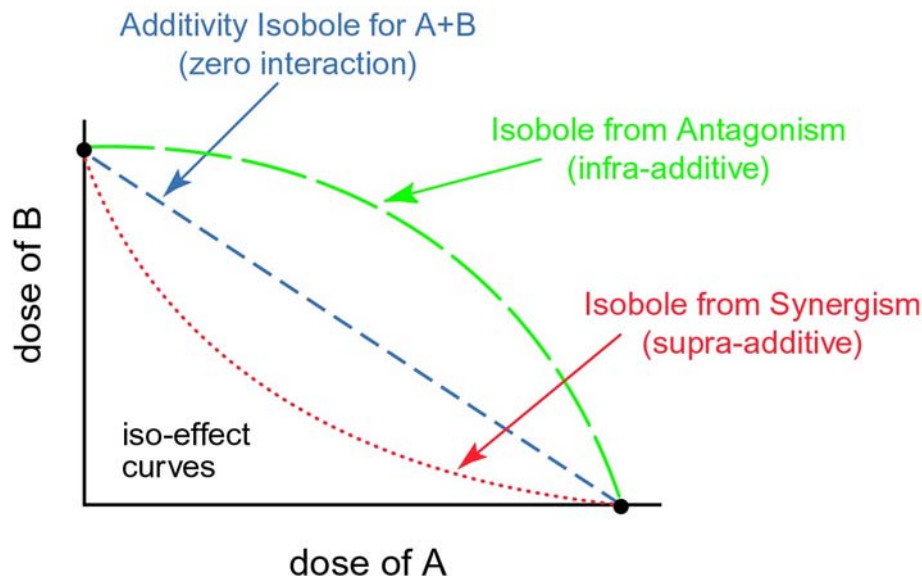
Hormesis: “paradoxical” effects at low concentrations





Isobologram – Plot of dose versus dose (for a binary mixture), where a pre-selected level of effect from the combined doses is always the same – “iso-effective” or “equi-effective” (e.g., 10% inhibition).

When the iso-effective doses of each agent alone (located along each axis) are connected via a line, this yields the line of “Loewe Additivity” or an “Additivity Isobole”.



The **Additivity Isobole** describes the combined binary doses that verify the hypothesis of no interaction [the simplest case results when both doses refer to the same compound].

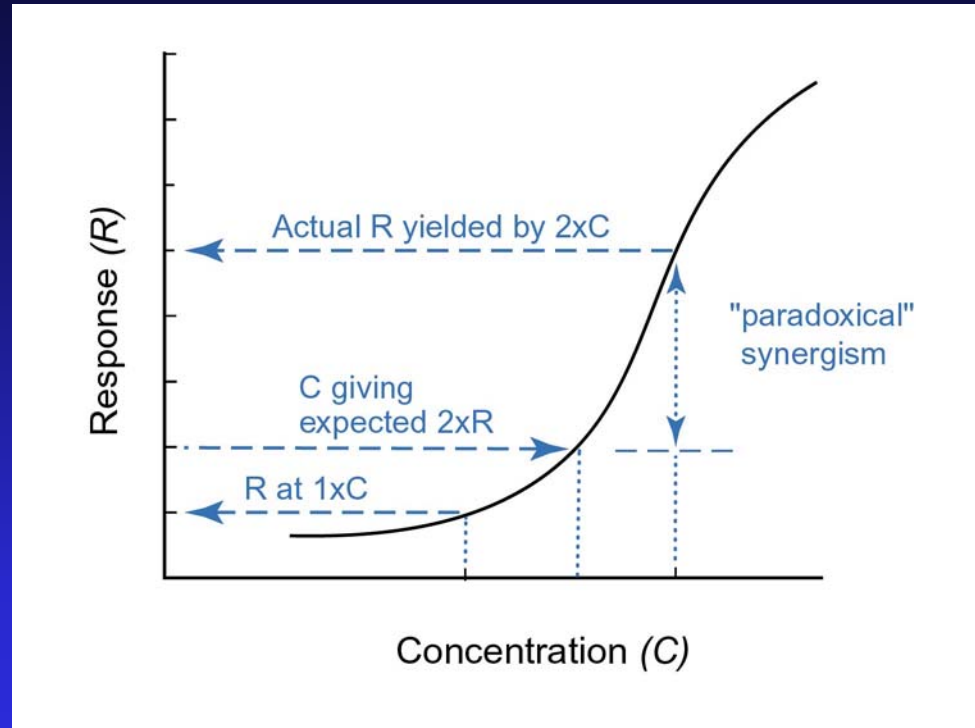
Combined binary doses described by non-linear curves residing off this line of “no interaction” verify interaction (combination effects).

Interactions involving antagonism reside above the additivity isobole line [these are usually concave).

Interactions involving synergism reside below the additivity isobole line [these are usually convex].

Complex Mixtures and Interaction/Combination Effects:

“Paradox” of *Effect Summation*



Effect summation valid only for linear curve portions extrapolating through origin.

Necessity of knowing responses for multiple doses – alone and in combination.

Note: middle line – *C giving expected 2xR* – is the erroneous result of “effect addition”.

top line – *Actual R yielded by 2xC* – is a valid result of “concentration addition”.

– *concluded* –

Unintended, Unexpected Effects

- Adverse (idiosyncratic) drug reactions in humans can be caused by previously unrecognized drug-receptor interactions, previously unidentified receptors, and by a broad diversity in drug-metabolizing/transport phenotypes (genetic polymorphisms).
- These variables are even more poorly characterized in aquatic biota.
- Just as animal models are frequently called into question for their relevance to human health, likewise, human and other mammalian toxicity data (e.g., from PPCPs) are not necessarily transferable to aquatic organisms.
- The use of certain drugs during critical times of development for fetuses, infants, and children is severely restricted because of the potential for serious adverse effects — timing of exposure with developmental stage is critical. These same drugs, however, if delivered to the aquatic environment, would enjoy no restrictions to prevent the exposure of developing non-target organisms.

Toxicological Endpoints – The need to expand the horizon?

- Up to recently, the historical primary endpoints of interest in risk assessment have been acute toxicity and carcinogenesis — little attention has been paid to the universe of other endpoints through which toxicants can exert their action.
- Other endpoints, such as neurobehavioral, immunological, and endocrine homeostasis alterations, can be very subtle but nonetheless lead to unanticipated, profound outcomes.
- Subtle endpoints could also be effected by extremely low concentrations of a toxicant (difficult to empirically test).
- Effects mediated (e.g., via hormone-like compounds) do not necessarily follow the monotonic sigmoid dose-response curve (U- and inverted-U-shaped curves can occur).

continued –

Toxicological Endpoints (cont'd)

- Effects on non-target organisms could differ between (and within) each class of PPCPs – the receptors being different for antimicrobials, endocrine modulators, SSRIs, antineoplastics, etc.
- This fact, coupled with a large spectrum of species (both aquatic and terrestrial) that could experience exposure, means that a very large array of toxicity screening procedures could be needed — prospects for a single apical assay are low.
- Accounting for wild-type drug-metabolism/transport polymorphisms further complicates any screening approach.
- Conventional toxicity testing does not address the ability (resiliency) to recover from repeated, cumulative chemical insults that slowly diminish the capacity to rejuvenate.

continued –

Toxicological Endpoints (cont'd)

- The priorities for selecting PPCPs for toxicological evaluation can NOT be based on their relative rankings of environmental concentrations simply because drugs can dramatically vary with respect to the concentrations at which they impart effects — sometimes by orders of magnitude.
- Response thresholds can be much lower for real-world chronic exposure (e.g., free, wild fish) than for short-term study exposures (e.g., for caged fish). Responses can be a function of not just the dose, and timing of dose, but also duration of exposure. Response thresholds (no-effect concentrations) can be continually reduced as exposure times increase.

Significant Distinction between Human Toxicology and Ecotoxicology

- ▶ Whereas human toxicology deals with responses at the cellular level or at the level of the individual, **ecological toxicology must ultimately deal with the much more complex levels of populations, communities, or ecosystems.**
- ▶ Indirect effects of chemical stressors can result from changing community composition (assemblage of species and their population ratios), such as via altered predation or competition or by leading to unanticipated “cascades” of changes that cannot be ascribed to the original event.
- ▶ Perhaps the emphasis should be on important “**functions**”, “**processes**”, or “**abilities**” (e.g., pollination, nitrification, dehalogenation, etc.) rather than collections of individuals, such as populations?

continued –

Ecological Effects:

Only significant at the population level?

- ▶ Ecological dogma maintains that ecological effects have significance ONLY if they impact the level of the population/community.
- ▶ While the rationale for this seems straightforward, its practical utility in terms of a guiding principal for ecotoxicology is of limited value.
- ▶ The temporal connection between cause and effect has the potential for being of such long duration that the linkage between cause and effect escapes detection or understanding.
- ▶ Continual exposure that causes but a gradual and ongoing diminution of a certain function or ability for a portion of individuals across multiple generations (in such a way that the effects at the population level are of no immediate consequence) may not be detected as connected with eventual population effects.
- ▶ Combination of specific, narrow windows of vulnerability and long latency periods confound epidemiological studies.

- concluded -

Factors complicating predictive assessment of which PPCPs (and significant metabolites) have the Highest Potential for Disposition to Sanitary Waste Systems or the Environment

- Data for a rational approach to ranking those PPCPs that have the highest probability of being released to the environment (without regard to overall toxicity) are largely lacking.
- Environmental surveys for PPCPs (using a target-analyte approach) can be guided in part by ranking their expected prevalence in STW influents, or better yet, STW effluents.
- But expected prevalence must also be considered in light of expected toxicity to assess those environmental concentrations that might prove significant .
- Two major factors must be known for each PPCP:
 - (1) individual's (or population's) usage/consumption rate,
 - (2) elimination efficiency (degree to which the parent compound and significant metabolites leave the body and enter sanitary systems).

Factors complicating determination of Usage/Consumption

- For external-use personal care products (which in general are not subject to metabolic alteration), there are few complicating issues. A straightforward determination can be made of the numerous ingredients that might be bioactive and then using industry production figures for combined members of each consumer-chemical “class”.
- In contrast to personal care products that are used externally, for medicinals the objective is exceedingly complex because production figures are largely confidential and because of the multitude of factors that affect the amount of drug ultimately eliminated from the body after internal dosing.
- Prescriptions filled and amounts consumed are difficult to acquire†; usage figures for regional/local levels may be proprietary (and the types of drugs can vary from municipality to municipality, county to county, region to region, and from country to country, and according to the age structure of the populations).†

continued –

Factors complicating determination of Usage/Consumption

† The first ever study of geographic variation across U.S. for prescription drug usage was completed and published by *Express Scripts* (2001).

This *Prescription Drug Atlas* is available at:

[http://www.express-scripts.com/
other/news_views/outcomes_research/atlas2002/atlas_ex_sum.htm](http://www.express-scripts.com/other/news_views/outcomes_research/atlas2002/atlas_ex_sum.htm)

But also must keep in mind that sales of drugs via the Internet may incur a substantial, unregulated import of unknown quantities of drugs from foreign countries. This also ought to be factored into (but is not) the total manufactured quantities used for calculating PECs‡ (which in turn ultimately determine if an ecological assessments is required for a new drug).

‡ PEC = predicted environmental concentration

continued -

Factors complicating determination of Usage/Consumption (cont'd)

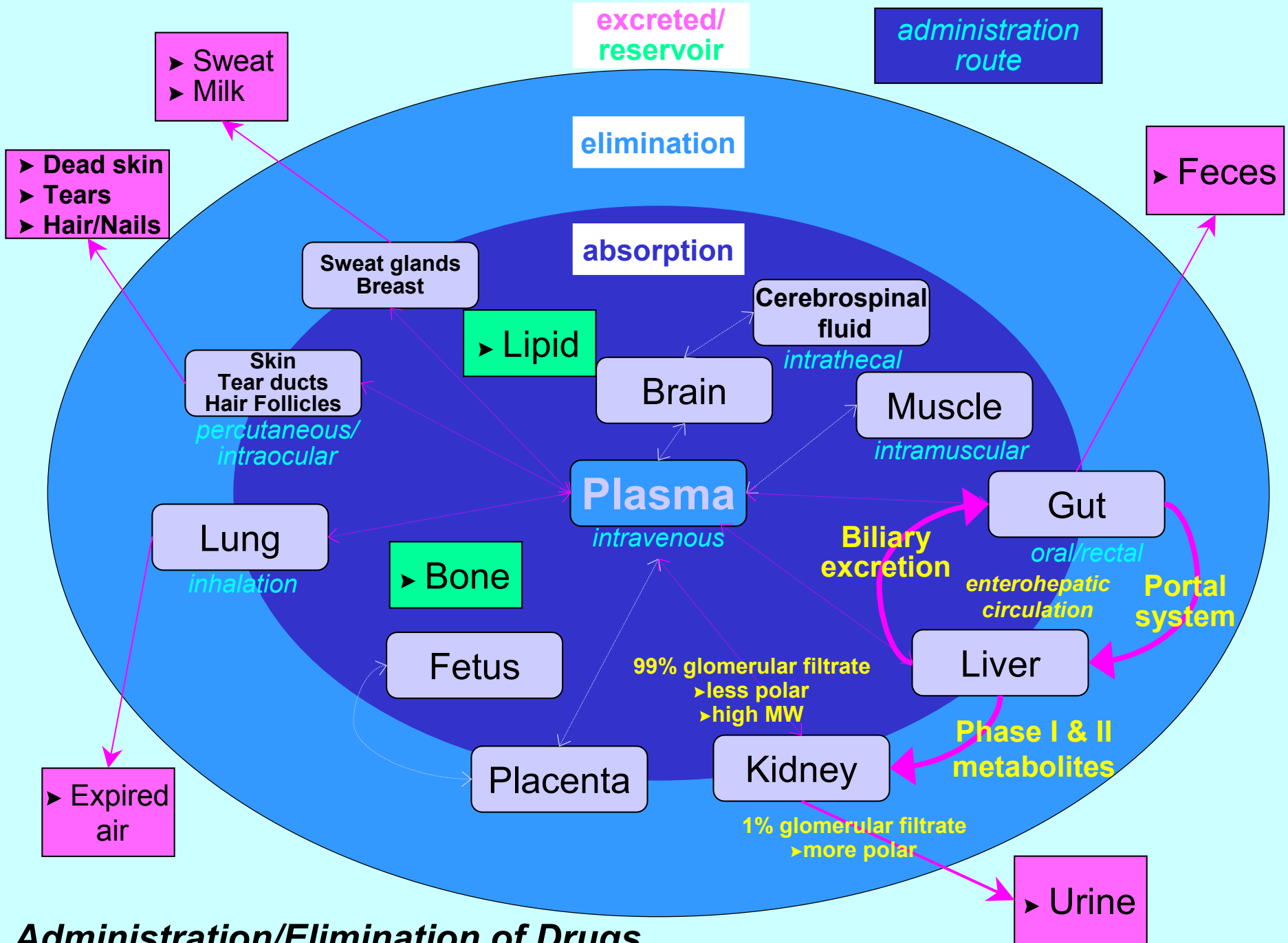
- Further complicating matters is that prescription numbers and OTC sales are only a rough measure of a drug's usage because they account for only a portion of the overall use.
- *Physician samples* and *black market sales* are other, sometimes substantial, sources that are difficult to account for.
- Countries also vary as to whether a drug is available by prescription or OTC (this could be significant for those drugs that have the potential to be transported across geographic boundaries).
- Together with usage, the efficiency with which a drug (or significant metabolite) is *eliminated* from the body is the second factor that determines the magnitude of its potential disposition to sanitary waste systems.

– *concluded* –

Factors complicating prediction of Drug Elimination from the Body

- The potential for an ingested drug to enter the environment is a function of its “elimination” in a bioactive state — which includes the parent drug together with its conjugates and significant metabolites.
- Elimination is the sum of the complex processes involved in the two major causes of drug loss from the body — metabolism and excretion.
- Pharmacokinetics (absorption, distribution, metabolism, and excretion — the ADME profile) plays a large but not exclusive role in determining the potential for a drug’s elimination.
- Long elimination (clearance) half-lives can mean that the extent of elimination has not been fully assessed during clinical trials (excretion can be more extensive than indicated from trials).

continued –



Administration/Elimination of Drugs

Factors complicating prediction of Drug Elimination from the Body (*cont'd*)

- While an idealized elimination profile can be established, it is always subject to profound deviations caused by numerous unexpected or undetected interacting variables (such as metabolic disorders), all of which can confound attempts to predict elimination efficiencies on a population level.
- For these reasons and many others, the ability to predict elimination is only possible within broad confidence bands. Resultant predicted or expected environmental concentrations that might be calculated from the literature can deviate substantially from reality. Deviations between predicted and actual elimination efficiencies can range from 0-100%.
- In the final analysis, it simply may not be possible to predict environmental occurrence rankings from the combined factoring of elimination efficiencies and prescription quantities, in which case any list of potential target analytes will be much larger.

ABSORPTION factors complicating prediction of elimination of drugs from the body

- First-pass metabolism, the mode of administration (e.g., enteral, parenteral, dermal), drug interactions, and other factors all affect absorption.
- For drugs that are easily metabolized, poor absorption from the gut (a direct function of overall health) can still lead to significant excretion of unaltered parent drug; elimination of parent drug can be further enhanced when suppositories are used.
- Adverse reaction factors can greatly increase elimination — gastrointestinal factors such as nausea/vomiting is common with many drugs; the emetogenic potential of some drugs is very high (e.g., from commonly prescribed drugs such as fluoxetine to the most highly controlled, such as cisplatin).
- The overall health profile of the end-user plays a large role in enhancing the excretion of unaltered drugs; e.g., any of various bowel diseases can greatly reduce absorption and thereby enhance excretion of unaltered drug (this in turn can be further affected by drugs that alter the motility of the gut – reducing or enhancing).

continued –

ABSORPTION factors complicating prediction of elimination of drugs from the body (*cont'd*)

- Drug's formulatary excipients (e.g., non-dissolving stearic acid tablets) may reduce absorption and thereby increase excretion of the unaltered parent drug far beyond expectations.
- Drug interactions with other chemicals and physiological condition can also dramatically reduce uptake and thereby enhance excretion of the parent drug; for example, chelation, alteration in gastrointestinal mobility, or alteration of gastric pH (e.g., chelation of tetracycline by dairy products or of fluoroquinolones by divalent cations).
- Dietary regime, time of day, division of doses (dosing schedules) all affect absorption and therefore excretion; the presence of food can delay or enhance the rate of absorption or alter metabolism.

METABOLISM factors complicating prediction of elimination of drugs from the body

An already complex issue can be yet further complicated by multiple dosing regimes:

- Pharmacokinetic interactions from concomitant/sequential dosing is difficult to assess.
- One drug can reduce the metabolism of another (e.g., via inhibition of any of the microsomal superfamily of cytochrome P450 isoenzymes), and consequently lead to increased excretion of the parent drug; or two drugs can work in concert to create an imbalance in metabolites (e.g., MAOIs and SSRIs leading to “serotonin syndrome” or “toxic serotomimetic reaction”).
- Not knowing the suite of medications that any individual is taking makes it even more difficult to predict excretion efficiencies.

continued –

METABOLISM factors complicating prediction of elimination of drugs from the body (*cont'd*)

- Age — younger and older patients are often on the tails of the metabolic “norm”.
- Older patients consume a large, disproportionate percentage of all prescription and OTC drugs.
- Genetics — distinct metabolic profiles caused by variations among individuals in enzyme concentrations and affinities, and isozyme ratios.
- Disease status — e.g., affect of urine pH on excretion of ionizable drugs.

EXCRETION/DISPOSAL factors complicating prediction of drug disposition to the environment

- The metabolic aspects involved with eventual drug excretion (primarily via the urine and feces) are extremely complex, involving the liver, gall bladder, kidney, and gut, among others (e.g., lungs, saliva, milk, etc.).
- In general, those drugs administered to patients with multiple illnesses, or those that are administered for severe disease states, will experience excretion efficiencies that deviate most markedly from predictions based on ADME studies.
- Poorly understood factors imposed by psychology are almost impossible to assess:
- Tendencies to abuse drugs (consume more frequent or higher doses than prescribed) can enhance excretion.
- Alternatively, noncompliance by the patient can result in prescribed courses of a particular drug to accumulate, leading to the expired/unused dosages to be disposed in the domestic sewage system.
- Are some PPCPs more prone to being disposed because they are prescribed or purchased in quantities too great to be used before expiration or because they tend to expire more rapidly?

– *concluded* –

Classes of PPCPs Identified in Environmental Samples

- In addition to antimicrobials and steroids, over 50 individual PPCPs or metabolites (from more than 10 broad classes of therapeutic agents or personal care products) have been identified (up to 1999) in environmental samples (mainly in sewage, surface, and ground waters). Database being extended by U.S. monitoring activities (e.g., USGS National Reconnaissance).
- It is important to note, however, that although a number of representatives from this subset of therapeutic classes have been identified in the environment, members of most classes have yet to be searched for.

continued –

Classes of PPCPs Identified in Environmental Samples

- The listings of PPCPs in the following tables are excerpted from two publications (where the supporting references can be found):

Daughton, C.G.; Ternes, T.A. “Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?” *Environ. Health Perspect.* 1999, 107(suppl 6), 907-938.
<http://www.epa.gov/nerlesd1/chemistry/ppcp/images/errata.pdf>

Daughton, C.G. “Pharmaceuticals in the environment: Overarching issues and overview,” in *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues*, Daughton, C.G. and Jones-Lepp, T. (eds.), Symposium Series 791; American Chemical Society: Washington, D.C., 2001, pp. 2-38.
<http://www.epa.gov/nerlesd1/chemistry/pharma/book-summary.htm>

- Note that since 1999, more PPCPs have been identified in various environmental samples.

continued –

PPCP Classes Identified in Environmental Samples

Representative classes (and members) of PPCPs reported in environmental samples.

therapeutic class	example Brand name	generic name
analgesics/ non-steroidal anti- inflammatories (NSAIDs)	Tylenol Voltaren Advil Oruvail Naprosyn	acetaminophen diclofenac ibuprofen ketoprofen naproxen
antimicrobials	many	e.g., sulfonamides, fluoroquinolones
antiepileptics	Tegretal	carbamazepine
antihypertensives (betablockers, beta- adrenergic receptor inhibitors)	Concor Lopressor	bisoprolol metoprolol
antineoplastics	Cycloblastin Holoxan	cyclophosphamide ifosfamide
antiseptics	Igrasan DP 300	triclosan
contraceptives	Oradiol	17 α -estradiol 17 α -ethinyl estradiol
β 2-sympathomimetics (bronchodilators)	Ventolin	albuterol
lipid regulators (anti- lipidemics; cholesterol- reducing agents; and their bioactive metabolites)	Atromid-S Lopoid	clofibrate (clofibric acid metabolite) gemfibrozil
musks (synthetic)	musk xylene Celestolide substituted amino nitrobenzenes	nitromusks polycyclic musks reduced metabolites of nitromusks
anti-anxiety/hypnotic agents	Valium	diazepam
sun screen agents	Eusolex 6300	methybenzylidene camphor
X-ray contrast agents	Hypaque	diatrizoate

Majority of PPCP classes have no environmental survey data

- Environmental survey data have yet to be reported for many classes (and class members) of PPCPs.
- While the literature is silent regarding these PPCPs, is this because of an absence of data or a failure to report “data of absence”?
- Many of these unreported drugs are among the most widely prescribed in the U.S.

continued –

PPCPs with no environmental survey data

Representative distinct classes of drugs for which concerted environmental surveys have not been performed

(bolded names among top 200 most prescribed in U.S.: <http://www.rxlist.com/top200a.htm>)

therapeutic class	example generic names (many drugs cross over into multiple classes)	example Brand names
adrenergic receptor inhibitors (anti-BPH agents)	terazosin , doxazosin , finasteride	Hytrin, Cardura, Proscar/Propecia
amyotrophic lateral sclerosis	riluzole	Rilutek
analgesics (non-NSAIDs and narcotic)	tramadol , propoxyphene , oxycodone , hydrocodone	Darvon, Ultram, Tylox
anorexiant (diet drugs)	fenfluramine, orlistat	Pondimin, Xenical
antiarrhythmics	disopyramide, flecainide, amiodarone, sotalol	Norpace
anticoagulants	warfarin	Coumadin
antidepressants	esp. SSRIs (sertraline , paroxetine , fluoxetine , fluvoxamine), tricyclics (desipramine), MAOIs (phenelzine), misc.	Zoloft, Paxil, Prozac, Luvox, Wellbutrin (bupropion), Serzone (nefazadone), Effexor (venlafaxine)
antidiabetic agents	insulin sensitizers, antihyperglycemic (e.g., sulfonylureas)	Rezulin (troglitazone), Glucophage (metformin), Glucotrol (glipizide), DiaBeta (glyburide)
antihistamines (H-1 blockers)	fexofenadine , loratadine , cetirizine , terfenadine	Allegra, Claritin, Zyrtec, Seldane

PPCPs with no environmental survey data

cont'd: Classes of Drugs Lacking Concerted Environmental Surveys

histamine (H-2) blockers	famotidine, ranitidine, nizatidine	Pepcid, Zantac, Axid
decongestants	ephedrines	
anti-infectives	many special disease classes (amebicides, anti-fungals, malarials, tuberculosis, leprosy, viral) & chemical classes	Diflucan (fluconazole)
antimetabolites	methotrexate	Rheumatrex
antipsychotics, CNS agents	alprazolam, zolpidem, clonazepam, risperidone, temazepam thioridazine, rifluoperazine	Xanax, Ambien, Klonopin, Risperdal, Restoril
calcium-channel blockers	diltiazem, nifedipine, amlodipine, verapamil	Cardizem, Procardia, Norvasc
digitalis analogs	digoxin , digitoxin	Lanoxin
diuretics	thiazide (hydrochlorothiazide , chlorthalidone); loop (furosemide, bumetanide); potassium-sparing (spironolactone, triamterene)	Lasix (furosemide) Dyazide (hydrochlorothiazide, triamterene)

PPCPs with no environmental survey data

cont'd: Classes of Drugs Lacking Concerted Environmental Surveys

dopamine agonists	anti-Parkinsonian agents (e.g., pramipexole, ropinirole)	Mirapex, Requip
expectorants	guaifenesin	Entex
gastrointestinal agents (ulcer drugs)	omeprazole, lansoprazole, cimetidine	Prilosec, Prevacid, Tagamet
HIV drugs	protease inhibitors, anti- retrovirals (nucleoside analog reverse transcriptase inhibitors)	Crixivan (indinavir), Retrovir (zidovudine)
hormonally active agents androgens anti-acne agents adrenocortico- steroids inhalable steroids estrogen antagonists	flouxymesterone isotretinoin, tretinoin prednisone, triamcinolone fluticasone tamoxifen	Accutane, Retin-A Flovent Nolvadex
muscle relaxants	cyclobenzaprine	Flexeril
osteoporosis agents	alendronate sodium	Fosamax
prostaglandin agonists	latanoprost	Xalatan

PPCPs with no environmental survey data

concluded: Classes of Drugs Lacking Concerted Environmental Surveys

psychostimulants (amphetamine-like)	methylphenidate, dextroamphetamine	Ritalin
sexual function agents	sildenafil citrate	Viagra
street drugs (illicit, illegal, recreational)	many: e.g., see listing at: "Streetdrug.org" (http://www.mninter.net/%7epublish/index2.htm)	
vasodilators (esp. angiotensin converting enzyme [ACE] inhibitors)	lisinopril, enalapril, quinapril, benazepril losartan, fosinopril, ramipril	Zestril, Vasotec, Accupril, Lotensin Cozaar, Monopril
newly approved, upcoming, and investigational drugs	Ongoing: see listing at: "Lexi-Comp.org" (http://www.lexi.com/new_drugs.htm)	
"chemosensitizers", efflux pump inhibitors (EPIs)	verapamil (and others from diverse classes; e.g., http://www.microcide.com/ICAAC99 Posters/icaac99_posters.html)	

Nationwide studies relevant to potential for PPCP occurrence and distribution in the environment

- 1999-2000: USGS implemented **first-ever U.S. national reconnaissance of “emerging pollutants” in waters**
 - objective was to establish baseline occurrence data
 - included were some commonly used PPCPs
 - data collected from 142 streams, 55 wells, 7 effluents (in 36 states)
 - findings published in 15 March 2002 issue of:
Environmental Science and Technology
 - detailed information available at:
<http://toxics.usgs.gov/highlights/whatsin.html>
- 2001: **first-ever study published on geographic variation** (across U.S.) **of prescription drug usage:**
Prescription Drug Atlas (Express Scripts, 2001), available at:
http://www.express-scripts.com/other/news_views/outcomes_research/atlas2002/atlas_ex_sum.htm

Significance of the USGS Monitoring Study

- The PPCPs documented in the USGS study to occur in US surface waters probably represent but a fraction of all those that actually occur.
- Whether the potential for health effects from this subset of PPCPs is eventually demonstrated is in large part irrelevant.
- More importantly, these occurrence data demonstrate the potential for ANY consumer-use chemical to enter the environment, and thereby **give us the advance opportunity to be watchful regarding the future introduction to commerce of drugs with new mechanisms of action and ever-increasing biochemical potencies.**

Ramifications of Geographic Variability in Drug Usage

- Environmental assessments for approving NDAs (new drug applications) are required by the U.S. FDA only when the concentration of a drug predicted to enter the aquatic environment (environmental introduction concentration, EIC) would be **1 ppb or greater**. [FDA's historical toxicity data for standard aquatic tests demonstrate no conventional effects at concentration less than 1 ppb]
- But calculation of the EIC assumes a uniform usage of a drug across the U.S. Data from the *Prescription Drug Atlas* (Express Scripts, 2001) show that for some drugs, regional preferences in usage can vary by several fold. This means that for highly populated metropolitan areas with usage of a particular drug exceeding what would be expected by a normal distribution, the **EIC could be higher than predicted**.

NOTE

Because of the size of this presentation, this file comprises only the 3rd part of the entire PPCPs slide presentation. The subsequent parts must be accessed separately.

Continue with part 4...